



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 December 2018
EMA/CVMP/EWP/77872/2018
Committee for Medicinal Products for Veterinary Use (CVMP)

Questions and answers on the CVMP guideline on the “Guideline on veterinary medicinal products controlling *Varroa destructor* parasitosis in bees” (EMA/CVMP/EWP/77872/2018)

The aim of this document is to provide clarification on some aspects of the CVMP Guideline on veterinary medicinal products controlling *Varroa destructor* parasitosis in bees (EMA/CVMP/EWP/459883/2008), which was published in 2010.

Question 1:

How should follow-up treatment be conducted?

Answer:

According to the guideline on veterinary medicinal products controlling *Varroa destructor* parasitosis in bees (EMA/CVMP/EWP/459883/2008), a ‘critical test’ should be employed to assess the efficacy of a candidate product. The extent of mite mortality after treatment with the candidate product should be determined using a follow-up treatment in the treated colony and placebo treated colony. This follow-up treatment should be with a chemically unrelated substance with >95% documented efficacy and carried out at the same time.

With regard to evaluation of efficacy, the aforementioned guideline states that the level of mite reduction after treatment should preferably be 95% or higher for synthetic substances. However, even if a product was granted a marketing authorisation on this basis, it does not necessarily follow that it is an appropriate choice for the follow-up treatment under all circumstances. For example, resistance to pyrethroids (e.g. tau-fluvalinate, flumethrin) has been reported in a number of Member States since the 1990s (Trouiller, 1998). Therefore, before a field study is initiated, applicants should ensure that mites within a representative number of hives in the participating apiaries are susceptible to the active substance within the intended follow-up treatment. The number of hives (from which mites are tested) per apiary should be based on statistical considerations, the origins of the hives, their treatment history and colony strength. Simply stating that the follow-up product contains a synthetic substance



and was authorised in accordance with guideline EMA/CVMP/EWP/459883/2008 is not sufficient; otherwise, a downward drift in the efficacy of new products may occur.

Methods for assessing the susceptibility of varroa mites to acaricides have been described in published literature. The suitability of the selected method for evaluating acaricide susceptibility must be justified by the applicant. Methods include bioassays (i.e. laboratory-based *in vitro* or *in vivo* tests), which evaluate phenotypic resistance status, and DNA-based assays for detection of mutations. With regard to the latter, Gonzalez-Cabrera *et al.* (2013) described a single point mutation in mites from southern England; this resulted in an amino-acid substitution, namely L925V, within the *Varroa destructor* voltage-gated sodium channel that was associated with resistance to pyrethroids. In the Czech Republic, Hubert *et al.* (2014) reported that the amino-acid substitution L1002V combined with F1052L was present in mites that survived exposure to tau-fluvalinate. Indeed, it is possible that other mutations that confer reduced susceptibility or resistance exist, but are yet to be identified. As such, it is preferable that applicants use bioassays as a means to demonstrate the susceptibility of mite populations to the substance within the follow-up treatment.

Applicants may also consider the use of non-synthetic substances as the follow-up treatment provided that (a) evidence of efficacy consistently greater than 95% can be provided and (b) no resistance mechanisms to the substance in varroa mites have been described.

The selected follow-up treatment should be appropriate for the season during which use of the candidate product is intended; for example, oxalic acid would be an inappropriate choice if the intention is to administer the candidate product in the presence of brood.

Finally, it is noted that the product literature for some products provides different dosage regimens for the treatment of varroosis or for the diagnosis of this disease. Generally, the follow-up treatment should be administered according to the dosage regimen for the treatment of varroosis.

References:

Gonzalez-Cabrera *et al.* (2013). An amino acid substitution (L925V) associated with resistance to pyrethroids in *Varroa destructor*. *PLoS One*, **8**, e82941.

Hubert *et al.* (2014). Point mutations in the sodium channel gene conferring tau-fluvalinate resistance in *Varroa destructor*. *Pest Manag Sci*, **70**, 889.

Trouiller (1998): Monitoring *Varroa jacobsoni* resistance to pyrethroids in western Europe. *Apiologie*, **29**, 537.

Question 2:

How should safety of the candidate product in queens be evaluated?

Answer:

Current guidance states that studies to demonstrate that treatment does not lead to intolerable effects on the health and reproductive capacity of queens should cover the lifetime of queens (from egg stage to normal time of replacement). However, the productive lifespan of a queen tends to be two to three years and therefore this data requirement is no longer considered to be realistic. Should a colony fail during a two to three year period, establishing whether the cause was treatment related would prove to be difficult as colony loss can result from a multitude of factors, e.g. lack of adequate food stores, presence of other diseases. As such, it is considered sufficient to evaluate the health of the queen by direct observations over a shorter time during the trials (e.g. presence of queen), and to use indirect means to support queen tolerance over a longer time span, based on her ability for reproduction demonstrated by the strength of the colony, i.e. colony strength post-application of the candidate product (i.e. short-term effects, refer to section 6.2.1 of guideline EMA/CVMP/EWP/459883/2008) and colony development during the spring following treatment administration (i.e. longer-term effects, refer to section 6.3 of guideline EMA/CVMP/EWP/459883/2008).

For products intended to be administered on multiple occasions during the year, colony development in spring should be evaluated having administered all possible treatments, as outlined in the SPC, in the preceding year.